doi:10.1093/brain/awp181 Brain 2009: 132; 2850–2870 | 2850

BRAIN
A JOURNAL OF NEUROLOGY

Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability

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Post-concussion syndrome (PCS) can affect up to 20%–30% of patients with mild closed head injury (mCHI), comprising incomplete recovery and debilitating persistence of post-concussional symptoms. Eye movements relate closely to the functional integrity of the injured brain and eye movement function is impaired post-acutely in mCHI. Here, we examined whether PCS patients continue to show disparities in eye movement function at 3–5 months following mCHI compared with patients with good recovery. We hypothesized that eye movements might provide sensitive and objective functional markers of ongoing cerebral impairment in PCS. We compared 36 PCS participants (adapted World Health Organization guidelines) and 36 individually matched controls (i.e. mCHI patients of similar injury severity but good recovery) on reflexive, anti- and self-paced saccades, memory-guided sequences and smooth pursuit. All completed neuropsychological testing and health status questionnaires. Mean time post-injury was 140 days in the PCS group and 163 days in the control group. The PCS group performed worse on anti-saccades, self-paced saccades, memory-guided sequences and smooth pursuit, suggesting problems in response inhibition, short-term spatial memory, motor-sequence programming, visuospatial processing and visual attention. This poorer oculomotor performance included several measures beyond conscious control, indicating that subcortical functionality in the PCS group was poorer than expected after mCHI. The PCS group had poorer neuropsychological function (memory, complex attention and executive function). Analysis of covariance showed oculomotor differences to be practically unaffected by group disparities in depression and estimated intellectual ability. Compared with neuropsychological tests, eye movements were more likely to be markedly impaired in PCS cases with high symptom load. Poorer eye movement function, and particularly poorer subcortical oculomotor function, correlated more with post-concussive symptom load and problems on activities of daily living whilst poorer neuropsychological function exhibited slightly better correlations with measures of mental health. Our findings that eye movement function in PCS does not follow the normal recovery path of eye movements after mCHI are indicative of ongoing cerebral impairment. Whilst oculomotor and neuropsychological tests partially overlapped in identifying impairment, eye movements showed additional dysfunction in motor/visuospatial areas, response inhibition, visual attention and subcortical function.

Received February 25, 2009. Revised April 30, 2009. Accepted May 25, 2009. Advance Access publication July 16, 2009
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Poorer subconscious oculomotor function in the PCS group supports the notion that PCS is not merely a psychological entity, but also has a biological substrate. Measurement of oculomotor function may be of value in PCS cases with a high symptom load but an otherwise unremarkable assessment profile. Routine oculomotor testing should be feasible in centres with existing access to this technology.

Keywords: head injury; PCS; saccades; OSP; neuropsychological function

Abbreviations: ACC = Accident Compensation Corporation; ATI = absolute time index; BDI II = Beck Depression Inventory (2nd Ed.); D–KEFS = Delis–Kaplan Executive Function System; GCS = Glasgow Coma Scale; IRI = inter-response index; LOC = loss of consciousness; mCHI = mild closed head injury; OSP = oculomotor smooth pursuit; PCS = post-concussion syndrome; PTA = post-traumatic amnesia; PTSD = post-traumatic stress disorder; RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey Complex Figure Test; RHIFQ = Rivermead Head Injury Follow-up Questionnaire; RPSQ = Rivermead Post-concussion Symptoms Questionnaire; WAIS III = Wechsler Adult Intelligence Scale 3rd Edition; WMS III = Wechsler Memory Scale 3rd Edition; WTAR = Wechsler Test of Adult Reading

Introduction

Post-concussion syndrome (PCS) can affect up to 20%–30% of the patients who have suffered a mild closed head injury (mCHI) and comprises incomplete recovery and debilitating persistence of post-concussional symptoms. PCS commonly encompasses a variety of somatic (e.g. headaches, dizziness), cognitive (e.g. poor concentration, memory planning) and behavioural/emotional (e.g. irritability, mood swings) symptoms, the composition of which can differ between individuals (Carroll *et al*., 2004; Iverson, 2005; Anderson *et al*., 2006). These symptoms manifest within the first few hours or days after the initial injury, but then persist to a varying extent for weeks, months or even years post-injury, having a potentially devastating effect on a patient's life (Carroll *et al*., 2004; Iverson, 2005). PCS has been recognized as a defined clinical entity (The World Health Organization, 1992; American Psychiatric Association, 1994), although the term 'post-concussional disorder' rather than 'syndrome' is now often used in the literature. The presence of PCS commonly impacts on patients' daily activities and ability to return to work, and also has financial implications for healthcare providers, as many affected patients seek medical attention from a general practitioner or hospital. Commonly, they are referred to specialized clinics or rehabilitation providers for further evaluation and management. In addition to clinical and neurological evaluation, their assessment commonly includes neuropsychological testing to detect cerebral dysfunction consistent with the patients' claims. Sometimes, patients are referred for brain imaging. However, neural injury from mCHI is largely beneath the detection threshold of conventional clinical CT or MRI scans. More advanced MR imaging techniques, such as functional MRI, diffusion tensor imaging, MR spectroscopy and arterial spin labelling, may be better at detecting functional, structural or perfusion changes in the brain but these techniques are costly and not routinely available in a clinical setting. Studies have been able to demonstrate neural injury with concomitant cognitive problems and post-concussional symptoms after mCHI (Levin *et al*., 1992; Jacobs *et al*., 1996; McAllister *et al*., 1999; Radanov *et al*., 1999; Hofman *et al*., 2002), but correlations of imaging abnormalities with neuropsychological and symptomatic outcome in mCHI are inconsistent (McAllister *et al*., 2001; Bazarian *et al*., 2007; Lipton *et al*., 2008; Miles *et al*., 2008; Niogi *et al*., 2008; Wilde *et al*., 2008) and there is very limited evidence that brain imaging is able to reliably demonstrate abnormalities in the brain of patients with PCS. Similarly, neuropsychological testing after mCHI has been criticized for its poor potential to indicate the presence of dysfunction, being influenced by premorbid intelligence and other factors such as age, education, state of employment, socioeconomic status, depression, malingering and litigation (Iverson, 2005). Meta-analyses of neuropsychological outcome following mCHI (Binder *et al*., 1997; Schretlen and Shapiro, 2003) suggest that any decrements in cognitive functioning largely resolve within 1–3 months post-injury. Analyses of effect sizes have demonstrated that patients with mCHI have little or no significant measurable effects on cognitive functioning after the acute recovery period and test performances are almost indistinguishable from those of normal matched controls (Schretlen and Shapiro, 2003; Iverson, 2005). Accordingly, the ability to accurately detect cognitive decrements associated with a mCHI using neuropsychological assessment diminishes with the passage of time.

We considered that the quantitative assessment of eye movement function might be able to contribute to the assessment of patients with PCS. The cerebral structures concerned with the control of eye movements are well-mapped and form extensive and highly complex functional entities, incorporating cortical and subcortical structures as well as the cerebellum. Studies in populations with neural injury and neurodegenerative disorders have shown that eye movement control relates closely to the functional integrity of the brain (Pierrot-Deseilligny *et al*., 2004; Müri and Nyffeler, 2008; Sharpe, 2008) and eye movement paradigms have been routinely used in the field of cognitive neuroscience to study the role of factors such as attention, working memory, response inhibition, speed of information processing, predictive behaviour and (motor) planning (Olk and Kingstone, 2003; Pierrot-Deseilligny *et al*., 2004; Barnes, 2008; Gooding and Basso, 2008; Hutton, 2008; Müri and Nyffeler, 2008). There is a body of evidence indicating that mCHI has a direct and measurable impact on motor control, with eye movement function in particular relating closely to the functional status of the brain after mCHI (Heitger *et al*., 2002, 2004, 2005, 2006, 2007*a*, 2008; Halterman *et al*., 2006; McIntire *et al*., 2006; Parker *et al*., 2006; Suh *et al*., 2006*a, b*; Catena *et al*., 2007;

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DeHaan et al., 2007; Drew et al., 2007; Pearson et al., 2007). These motor deficits are independent of intellectual ability and occur independently of neuropsychological impairment after mCHI (Heitger et al., 2004). Research on the recovery profile of such oculomotor impairment after mCHI shows that deficits are most prevalent within the first week post-injury and then recover over the next 6 months, with most of this recovery occurring in the first 3 months post-injury (Heitger et al., 2006). In the present study, we examined whether PCS patients continue to show disparities in eye movement function at 3–5 months following mCHI compared with patients with good recovery, to our knowledge the first study to examine this question. We hypothesized that the assessment of eye movement function would provide sensitive and objective functional markers of ongoing cerebral impairment in PCS, supporting the presence of PCS independently of neuropsychological assessment and patient self-report.

Methods

Participants

All PCS participants were recruited through a local Concussion Clinic (Burwood Hospital, Canterbury District Health Board, Christchurch, New Zealand). Inclusion criteria for the PCS group were: aged 16–70, mCHI within the previous year (the preference was 'within the previous 6 months', although three PCS cases with a high symptom load, who were beyond 200 days post-injury, were accepted into the study), and having been referred to the Concussion Clinic after seeking medical attention for persistent post-concussional symptoms. Eligible participants had to have a Glasgow Coma Scale (GCS) of between 13 and 15 on first assessment (i.e. the first recorded GCS post-injury) without falling below 13 at any consecutive assessment. Participants whose initial GCS was not available but whose case history and injury mechanism was considered consistent with mCHI were eligible for the study. Post-injury disturbance of consciousness (if applicable) had to be <30 min and duration of post-traumatic amnesia (PTA) <24 h. Estimated PTA duration was established retrospectively at the time of study assessment following an iterative protocol applied in previous studies (Heitger et al., 2007*a, b*). Comments in participants' hospital files about the presence of PTA were taken into account when calculating an approximation of PTA duration. Potential participants were excluded if there was evidence of regular intake of psychoactive drugs or history of drug abuse, central neurological disorder or psychiatric condition.

Participants in the PCS group needed to have a sufficiently high level of post-concussional symptoms to be eligible. The criteria were based on diagnostic criteria of the WHO 10th International Classification of Diseases (The World Health Organization, 1992). The WHO criteria were chosen over those of the DSM-IV (American Psychiatric Association, 1994) in order to be able to examine neuropsychological status between our groups without introducing a recruitment bias that would have facilitated poorer neuropsychological performance in the PCS group. Current evidence suggests that there are essentially no differences in the outcome domains of psychiatric symptoms and disorders, social and community integration, health-related quality of life or global outcome between PCS patients diagnosed based on the WHO criteria and those identified using the DSM-IV criteria (McCauley et al., 2005).

The classification of PCS participants was primarily based on the scores on the Rivermead Postconcussion Symptoms Questionnaire (RPSQ) covering the WHO symptom categories 1–4. In accordance with the ICD-10 criteria, PCS participants had to have symptoms in at least three of the assessed symptom categories on the RPSQ. In order to be classified as 'positive' for a particular symptom category, a score of 2 or more on the RPSQ had to have been reported for at least one symptom in that category (i.e. the symptom was perceived at least as a mild problem). The RPSQ symptoms were assigned to the ICD-10 symptom categories as follows: Category 1 ('headache, dizziness, malaise, fatigue, noise intolerance') was represented by the RPSQ symptoms 'headaches, feelings of dizziness, nausea or vomiting, noise sensitivity and fatigue'. Category 2 ('emotional changes, irritability, depression, anxiety, emotional lability') was represented by 'being irritable/easily angered, feeling depressed or tearful, feeling frustrated or impatient'. Category 3 ('difficulty in concentration and in performing mental tasks, memory problems') was represented by 'forgetfulness/poor memory, poor concentration, taking longer to think' and Category 4 ('insomnia') was represented by the rating on 'sleep disturbance'. Participants were not rated on symptom Category 5 ('reduced alcohol tolerance') as many participants did not, according to their own account, have a regular alcohol intake or else were under the legal drinking age, thereby preventing a meaningful assessment of alcohol tolerance. Symptom Category 6 (pre-occupation with present symptoms, adoption of sick role and fear of permanent brain damage) was considered 'positive' by default due to the study recruitment bias, the PCS group having been recruited from a population of patients who suffer persistent post-concussional symptoms and perceive an adverse impact of these symptoms on their daily lives that is sufficient to seek medical attention for this problem.

In order to keep the study population 'relevant' and representative of the type of PCS cases commonly seen at Concussion Clinics, we discarded the WHO criterion of a required loss of consciousness (LOC) at time of injury. It is common to encounter patients attending these clinics who may not have suffered a LOC, or who may not remember whether there was a LOC, but who nevertheless report a high symptom load and poor ability to cope with activities of daily living as a result of their injury. Also, based on the WHO criteria, it is possible for a patient to have a high symptom load but for all symptoms to fall within the same one or two symptom categories. Hence, we accepted participants into the PCS group who only fulfilled two of the required three RPSQ symptom categories but met one or more additional criteria/conditions: (i) problems in the 5th symptom category on the RPSQ (light sensitivity/easily upset by bright light, blurred vision, double vision, restlessness); (ii) total of 16 or higher on the RPSQ and/or (iii) notable problems on activities of daily living on the Rivermead Head Injury Follow-up Questionnaire (RHIFQ) amounting to a total of $\geqslant 8$ with a score of $\geqslant 2$ on at least one item. A total of 8 on the RHIFQ is equivalent to 20% of the maximum attainable score and five times higher than the RHIFQ mean score of non-PCS patients at 3 months post-injury observed in previous studies (Heitger et al., 2006).

The control group for the present study was recruited from mCHI cases with good recovery and identified via a parallel research study examining the relationship between early eye movement function after mCHI (i.e. within the first 10 days post-injury) and recovery at 3 and 6 months. That study included 301 participants with mCHI who completed mailed follow-up questionnaires at 3 and 6 months post-injury, identifying a large pool of cases with mCHI and good recovery. Each control was individually matched as closely as possible to a PCS participant regarding age (max. ± 5 years if aged 20 and above, ± 2 years below age 20), gender, years of formal education (max. ± 5 years), time post-injury (as close as possible but no more than PCS participant's days post-injury $\times 2$) and then, if possible, injury

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cause and history of previous head trauma. Years of formal education was the total of all years of formal training including school years and any subsequent training such as apprenticeships and university study (results are given in 'full-time equivalents', i.e. 2 years part-time study equates to 1 year full-time). Highest completed formal qualification was rated for all participants by assigning scores of between 1 and 4 (attending/completing high school = 1, completed apprenticeship = 2, completed qualification at a Polytechnic or other non-university tertiary education institution = 3, completed university degree, regardless of Bachelor, Masters or PhD = 4). History of previous head trauma is a risk factor influencing the symptom resolution after head injury and we aimed to control for this factor wherever possible (i.e. after meeting the primary matching criteria, preference was given to suitable controls who also matched the history of previous head trauma, but this option was not always available). The principal criterion was a YES/NO classification regarding presence of any previous head trauma, regardless of how long ago. As previous medical records for the entire life span of our participants were not available, the history of head injury was confirmed by interviewing the participants at the time of assessment for the study (for participants in the control group, this information had been collected at the time of their first eye movement assessment conducted as part of a parallel study at ~1 week post-injury). Estimates on the severity of previous head trauma were assigned based on patients' recall of factors such as being told about the severity of their injury by the treating medical team, duration of required hospital stay (if attended at all), LOC, recall of significant memory loss following the historic injury, time to recover, memory of medical treatment and context of sustaining the historic injury. 'History of head trauma' referred to any head trauma sustained before the most recent one (i.e. in case of the PCS participants, the trauma which lead to ongoing complaints and subsequent referral to the Concussion Clinic, and in case of the controls, any historic head injury before the head injury sustained ~5 months prior to study inclusion). Based on the available information, we assessed history of single or multiple head injury, estimated the severity of the most severe historic head trauma (1 = mild, 2 = moderate, 3 = severe), and rated the time delay since the most recent historic head injury (4 = within the previous year, 3 = between 1 and 5 years prior, 2 = between 5 and 10 years prior, 1 = 10+ years prior).

Clinical services and other injury-related costs for the participants in the PCS group were covered by the New Zealand Accident Compensation Corporation (ACC), a government-funded public insurer. Every New Zealand resident is automatically insured by ACC. ACC operates on a 'no-blame' policy and will pay for medical treatment costs, post-injury assessments and provide monetary compensation to patients unable to return to work. Hence, entitlement to funding for clinical services and injury-related costs was uniform across subjects. To our knowledge, none of our participants were involved in any dispute or seeking monetary compensation beyond the standard provisions covered within the mandate of ACC. Any clinical services and injury-related costs in the control group were also covered by ACC, although in the control group this was only relevant in the early stage post-injury as all controls then made a complete and uncomplicated recovery (i.e. there were no concurrent injury-related costs for the participants in the control group at the time of study assessment). All study-related costs for the controls (i.e. travel costs and neuropsychological assessment) were paid for by ACC. Before participating in the study, all prospective participants were made aware that their future healthcare, including access to free public healthcare and coverage by ACC, would not be affected by their decision whether or not to take part in the study. Subjects were offered compensation for travel costs to attend the testing but received no other payment. The project was approved by the Canterbury Ethics Committee/Upper South A Regional Ethics Committee and written consent was obtained from all participants.

Oculomotor testing

The paradigm parameters and key measures were identical to earlier studies (Heitger *et al*., 2002, 2004, 2006, 2007*a*). We incorporated reflexive saccades ('looking at the stimulus', 44 saccades, stimuli jumping randomly by 5°, 10°, 15°, 20°, 25° or 30° in a horizontal direction, at intervals varying pseudo-randomly between 1.0 and 1.6 s), anti-saccades ('looking away from the stimulus to its mirror-location on the opposite side of the screen', 32 anti-saccades, stimuli at 5° and 15° off-centre, at intervals varying pseudo-randomly between 1.0 and 1.6 s, balanced for left and right), memory-guided sequences of saccades ('performing a memorized sequence of saccades', six different sequences, each with four steps, duration of 1.0 s per step, each sequence practised five times, then performed once, followed by presentation of the next sequence), self-paced saccades ('do-as-many-as-possible'-self-pacing for 30 s between two stationary targets, ± 15° off-centre) as well as sine and random oculomotor smooth pursuit (OSP) ('tracking a continuously moving target', sine OSP at 40° and 60°/s peak velocity, and random OSP at mean peak velocity 80°/s, each task 40 s duration). Eye movements were recorded using an IRIS infrared limbus tracker (Skalar Medical, BV, Delft, The Netherlands) (Reulen *et al*., 1988). Subjects were seated in a darkened room. Head movements were stabilized via a wax bite-bar. Eye movements were elicited by instructing the subject to follow computer-generated stimuli on a computer monitor (IBM P275 Colour Monitor) 45 cm in front of the subject (stimuli for saccadic tests: red/green square targets, subtending 0.75°; for OSP: a circle with a centred cross, subtending 4.82°). The tests were generated and controlled by a PC, which also recorded the data for off-line analysis. The equipment was calibrated at the start of the session and between tests. Before the tests, subjects' vision was checked on a reading/letter chart to ensure that visual acuity was sufficient for accurate test performance. It was also checked that subjects did not experience any visual disturbances (e.g. blurred vision or double vision) at the time of testing. Mean values of the key measures over all trials in a particular test paradigm were used in analyses. Before the test proper, subjects were shown an example of each paradigm in order to familiarize them with the task requirements. Key measures (per paradigm) were saccade latency (ms) (reflexive, anti- and self-paced saccades), saccade velocity (degrees/second) (reflexive, anti-saccade, self-paced saccades and memory-guided sequences), saccade duration (ms) (reflexive, anti-saccade, self-paced saccades and memory-guided sequences), saccade 'time-to-peak velocity' (ms) (reflexive, anti-saccade, self-paced saccades and memory-guided sequences), number of saccades made during memory-guided sequences, directional errors (anti-saccades, memory-guided sequences), number of self-paced saccades within 30 s, mean absolute position error of the final eye position and gain (eye position/stimulus position) of the primary saccade and final eye position (Heitger *et al*., 2004). For memory-guided sequences of saccades, amplitude errors were also derived (Heitger *et al*., 2002). For the memory-guided sequence task, we also calculated an 'absolute time index' (ATI = subject's total response time/duration of the sequence) and 'inter-response index' (IRI, measure for the subject's ability to maintain a constant rhythm during a sequence, centred around the optimum of zero) (Heitger *et al*., 2002). Key measures for OSP were the average eye peak velocity (degrees/second) after removal of all saccades from the tracking performance, tracking lag

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(ms), number of catch-up saccades and mean absolute tracking error (degrees).

Neuropsychological tests

All participants were assessed on the neuropsychological tests conducted as part of the standard evaluation at the local Concussion Clinic. These tests were the Digit Span, Similarities, Picture Completion and Digit Symbol subtests of the Wechsler Adult Intelligence Scale 3rd Edition (WAIS III) (Wechsler, 1997*a*), Wechsler Test of Adult Reading (WTAR) (Psychological Corporation, 2001), Rey Auditory Verbal Learning Test (RAVLT) (Lezak, 1983; Spreen and Strauss, 1998; Lezak *et al*., 2004), Rey Complex Figure Test (RCFT) (Meyers and Meyers, 1995; Lezak *et al*., 2004), Trail Making Test (Reitan and Wolfson, 1985; Spreen and Strauss, 1998), the Zoo Map Test of the Behavioural Assessment of Dysexecutive Syndrome (Wilson *et al*., 1996), the subtests Verbal Fluency Test and Colour-Word Interference Test of the Delis–Kaplan Executive Function System (D–KEFS) (Delis *et al*., 2001), the Logical Memory 1 and 2 subtests of the Wechsler Memory Scale 3rd Edition (WMS III) (Wechsler, 1997*b*) and the Beck Depression Inventory (2nd Edition) (BDI II) (Beck *et al*., 1996). Motivational factors were also clinically assessed for all participants to confirm that subject compliance and test effort on the neuropsychological tests was sufficient for study inclusion.

Health status questionnaires

Three health status questionnaires measured subjects' current health condition, level of post-concussional complaints and performance on everyday tasks. These measures were the SF-36 Health Survey (version 2) (Ware *et al*., 2000), the RPSQ (King *et al*., 1995) and the RHIFQ (Crawford *et al*., 1996). All were administered as written questionnaires. The questionnaires were completed at the time of the eye movement assessment, after completion of the eye movement tests. The assessment period for answers on the RPSQ was extended from 'the previous 24 h' to 'the previous 7 days'. This was also maintained for the RHIFQ. The standard form was used for the SF-36 v2.

Statistical analysis

Group comparisons between PCS and non-PCS participants were undertaken using a *t*-test for dependent samples. Effect size was defined by dividing the difference between the PCS and non-PCS group means by the standard deviation of the differences between the matched pairs. Pearson *R* coefficients were used to examine correlations between measures. A McNemar's chi-square test was used to examine group differences in frequency of PTA, LOC, previous history of head trauma and influence of alcohol at the time of injury. A *t*-test for independent samples was used to compare clinical measures of injury severity (duration of PTA and LOC) that differed between groups regarding number of subjects having experienced these factors. The associations of group differences in estimated full-scale WAIS-III IQ and depression on the BDI II with the group differences in eye movement performance and neuropsychological function were explored via analysis of covariance (Heitger *et al*., 2004). For all measures showing a significant influence of estimated IQ and/or depression, corrections were made to adjust for this influence. This study examined the effect of mCHI on a range of measures in the domains of oculomotor function, neuropsychological performance and self-reported health status. Whilst each of these domains contains a number of inter-correlated and thus, non-independent observations, the three separate domains are independent observational entities. Therefore, we applied a statistical correction to the group comparisons and the associated analyses of covariance in these three domains by reducing the level at which results were considered significant to a two-tailed $P \leqslant 0.0166$ (i.e. 0.05/3). The observations of group differences between the PCS and non-PCS group with regard to age, gender, education, previous history of head trauma and clinical measures of injury severity such as GCS, LOC and PTA were a direct consequence of the recruitment bias for this study and are not an independent (functional) test category. For this reason, and because of the importance of being able to detect any group disparities with regard to matching PCS and non-PCS participants, we maintained a two-tailed $P \leqslant 0.05$ for these parameters.

Results

Study groups

The study comprised 36 participants in each group (Table 1). Thirty participants in the PCS group met the primary study inclusion criteria based on the adapted WHO guidelines. The remaining PCS participants had only two 'positive' symptom categories on the RPSQ but qualified for study inclusion due to meeting the additional criteria. Clinical data on post-injury hospital treatment was available for 50% of participants in the PCS group and for all the controls. For 18 participants in the PCS group, no clinical data were available covering the early time period post-injury. The majority of these participants did not seek medical attention for their injury at the time but attended a GP days or weeks later. Eleven participants in the PCS group had a confirmed LOC. In another eight PCS cases, LOC was likely, based on the known history. However, the duration of LOC could only be established in eight PCS participants. In comparison, 20 controls had a confirmed LOC and another three a likely LOC (duration of LOC was known for 19 controls). The mean LOC duration for 'known' cases was longer in the PCS group ($P = 0.023$). PTA had been experienced by 23 PCS participants and 17 controls ($P = 0.263$), with no significant contrasts in PTA duration. There was no group difference regarding number of cases with influence of alcohol at time of injury. Similarly, there was no group difference in number of participants with previous history of head trauma. Incidence/severity of previous head trauma and time delay since last historic head injury were balanced across the groups. There were six participants in each group who had a history of multiple head trauma. Most participants with a history of head trauma had a history of mild head injury only (PCS group: mild—13, moderate—3, severe—1; Controls: mild—11, moderate—2, severe—1). The case of severe head trauma dated back >10 years in both groups. In the PCS group, the most recent moderate head trauma was in the 5–10 years range. In the control group, the two moderate cases of historic trauma fell into the 2–5 year and 5–10 year ranges. There were no group differences for time delay since the last historic head trauma (PCS mean ± SD versus Non-PCS mean ± SD: 2.35 ± 1.22 versus 2.21 ± 1.12, $P = 0.75$) or the mean injury severity of the most severe historic head trauma (1.29 ± 0.59 versus 1.28 ± 0.61, $P = 0.97$).

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Table 1 PCS versus non-PCS—group characteristics

	PCS group ($n=36$)	Non-PCS group ($n=36$)	P-value
Age at time of injury, mean (SD)	38.0 (14.1)	37.9 (14.3)	0.866
Years of formal education (high school + later training) , mean (SD)	14.5 (3.1)	14.8 (2.5)	0.511
Rating for highest completed formal qualification, mean (SD)	2.2 (1.1)	2.6 (1.1)	0.102
Gender (F/M)	16/20	16/20	
Eye movements—time since injury (days) , mean (SD)	140.3 (51)	163.2 (48)	0.002
Neuropsychological assessment—time since injury (days) , mean (SD)	140.2 (50)	162.8 (47)	0.003
Number of patients with initial GCS 13	0	3	
Number of patients with initial GCS 14	6	6	
Number of patients with initial GCS 15	12	27	
GCS not available (went to GP, attended hospital in different city, no medical attention sought)	18	0	
Score of initial GCS (= first recorded GCS) , mean (SD)	14.7 (0.5)	14.7 (0.6)	0.381
Score of GCS at 6h after first recorded GCS, mean (SD)	14.9 (0.3)	14.9 (0.3)	0.178
Number of patients with PTA	23	17	0.263
PTA duration amongst patients with PTA (min) , mean (SD)	160 (330)	91 (104)	0.417
PTA duration Median (quartiles)	*20 (5.0/120)*	*30 (10.0/210)*	
Number of patients with confirmed LOC	11 (duration known in 8 cases)	20 (duration known in 19 cases)	0.152
LOC unconfirmed but deemed likely	8	3	
No LOC	17	13	
LOC duration amongst patients with LOC (min) , mean (SD)	8.1 (10.2)	2.1 (2.5)	0.023
LOC duration Median (quartiles)	*3 (1.5/12.5)*	*1.0 (0.5/3.0)*	
Number of patients with influence of alcohol at time of injury	4	10	0.228
Number of patients with history of prev. head trauma	17	14	0.502
Injury causes			
Falls (e.g. off-ladder, tripped and fell, etc.)	12	13	
Motor vehicle accident	7	3	
Walk/stand + hit (i.e. people walking into obstacle or standing up and hitting their head)	4	1	
Sports (PCS = rugby, skateboarding, Controls = horse-riding, rugby, soccer)—mostly of 'fall' nature	2	8	
Assault	5	4	
Bicycle accident (no other vehicles involved)	3	6	
Cyclist versus car	1	1	
Pedestrian versus bicycle (run over by bicycle)	1		
Pedestrian versus Car	1		

The distribution of injury causes was similar for both groups. Two participants in the PCS group were unemployed at the time of testing. All other participants were either employed or attended institutions for secondary or tertiary education.

Health status, activities of daily living and quality of life

Consistent with the selection criteria for the study, the PCS group differed markedly from the non-PCS group on the health status measures (Table 2). All group differences were highly significant at $P<0.001$, with exception of double vision on the RPSQ.

Neuropsychological measures

The initial group comparison of the neuropsychological test results showed poorer performance of the PCS group on all subtests of the WAIS III, the WTAR, WTAR-based predicted full-scale WAIS-III IQ, several subtests of the D–KEFS, the WMS III, Trail Making A and B and the RAVLT Distractor list. There also was a marked group difference on the BDI II (Table 3).

A group difference in the WTAR-based predicted full WAIS-III IQ (WAIS-III FSIQ) was unexpected as mCHI may alter the performance on IQ tests in the short term but this should not be a lasting effect. The finding of an apparently lower predicted WAIS-III FSIQ in the PCS group at almost 5 months post-injury suggested that the observed group difference may have been due to an unexpected selection bias with the control group having a higher IQ. We therefore used analysis of covariance to further explore whether the poorer neuropsychological performance was associated with this group difference in estimated IQ. Since incidence of depression may influence test behaviour and motivation for optimal performance, we also examined whether the strong contrast in depression on the BDI II influenced any of the observed neuropsychological differences.

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Table 2 PCS versus non-PCS—self-perceived health status

Measure	PCS group ($n=36$) Mean (SD)	Non-PCS group ($n=36$) Mean (SD)	*P*-value
SF-36 health survey—scales[a]			
Physical function	78.33 (17.97)	96.39 (8.33)	0.000001
Role-physical	44.79 (28.17)	97.40 (6.74)	<0.000001
Bodily pain	61.56 (27.28)	87.33 (15.53)	0.00002
General health	66.53 (21.02)	83.89 (13.02)	0.0002
Vitality	36.98 (16.26)	70.83 (16.77)	<0.000001
Social function	49.65 (24.36)	95.83 (8.96)	<0.000001
Role-emotional	58.33 (29.41)	96.06 (8.33)	<0.000001
Mental health	60.69 (19.72)	83.06 (10.91)	<0.000001
Physical summary score	46.29 (7.54)	56.45 (4.52)	<0.000001
Mental summary score	36.37 (11.56)	54.04 (6.29)	<0.000001
RPSQ[b]			
Total score	26.19 (10.55)	4.83 (4.98)	<0.000001
Headaches	1.72 (1.26)	0.47 (0.65)	0.00001
Dizziness	1.19 (1.06)	0.28 (0.57)	0.0001
Nausea/vomiting	0.81 (1.06)	0.06 (0.23)	0.0003
Noise sensitivity	1.47 (1.08)	0.31 (0.62)	0.00002
Sleep disturbance	1.94 (1.31)	0.67 (0.83)	0.0001
Fatigue/tiring more easily	2.64 (1.02)	0.61 (0.80)	<0.000001
Irritability/easily angered	2.11 (1.24)	0.39 (0.64)	<0.000001
Feeling depressed	1.47 (1.18)	0.28 (0.57)	0.000004
Frustration/Impatience	2.03 (1.21)	0.39 (0.64)	<0.000001
Forgetfulness/poor memory	2.11 (0.92)	0.39 (0.64)	<0.000001
Poor concentration	2.31 (0.86)	0.22 (0.48)	<0.000001
Taking longer to think	2.42 (0.91)	0.31 (0.62)	<0.000001
Blurred vision	0.78 (0.96)	0.14 (0.35)	0.0008
Light sensitivity	1.42 (1.32)	0.11 (0.32)	0.000003
Double vision	0.28 (0.81)	0.03 (0.17)	0.0831
Restlessness	1.50 (1.16)	0.19 (0.40)	<0.000001
RHIFQ[c]			
Total score	16.72 (8.03)	1.14 (2.40)	<0.000001
Conversation with one person	1.00 (0.89)	0.03 (0.17)	
Conversation with two or more	1.78 (1.05)	0.08 (0.28)	<0.000001
Routine domestic activities	1.47 (1.11)	0.03 (0.17)	<0.000001
Participation in prev. social act.	1.81 (1.31)	0.11 (0.40)	<0.000001
Enjoying prev. leisure activities	1.72 (1.23)	0.14 (0.49)	<0.000001
Maintaining prev. work load	2.44 (1.16)	0.17 (0.45)	<0.000001
Finding work more tiring	2.69 (1.09)	0.42 (0.69)	<0.000001
Relationships with prev. friends	1.19 (1.14)	0.08 (0.37)	0.00001
Relationship with partner	1.00 (1.26)	0.00 (0.00)	0.00004
Coping with family demands	1.61 (1.20)	0.08 (0.28)	<0.000001

a High scores on the SF-36 scales represent better status (max.: 100, summaries centred around 50).
b Low scores on the RPSQ represent better status (max. total score: 64, symptoms scored 0–4).
c Low scores on the RHIFQ represent better status (max. total score: 40, symptoms scored 0–4).

We found associations between the group difference in estimated WAIS-III FSIQ and several of the neuropsychological impairments including measures of the WAIS III, D-KEFS and Trail Making. In all cases, no significant group differences remained after controlling for the difference in estimated intellectual functioning between the groups (Table 4). There was no association between the group difference in depression and any of the neuropsychological impairments. There also was no association between estimated WAIS-III FSIQ and depression ($\beta=0.11$, $P=0.53$). The mean effect size of all remaining neuropsychological group differences was 0.56 (Fig. 1).

Oculomotor measures

The PCS group had higher numbers of directional errors on anti-saccades and memory-guided sequences (Table 5). On anti-saccades, the gain of the final eye position was hypermetric compared with controls. The PCS group exhibited larger absolute position errors of the final eye position in anti-saccades and memory-guided sequences, and a larger final amplitude error in memory-guided sequences. In memory-guided sequences, the PCS group made a significantly higher number of saccades in Step 3, with a marginally increased number of saccades in Step 1. In the

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Table 3 PCS versus non-PCS—Neuropsychological performance

Measure	PCS group ($n=36$) Mean (SD)	Non-PCS group ($n=36$) Mean (SD)	*P*-value
Wechsler Adult Intelligence Scale-III (age scaled scores)			
WAIS III Digit Span	9.3 (2.0)	10.4 (1.7)	0.027
WAIS III Similarities	10.0 (2.1)	11.2 (2.2)	0.007
WAIS III Picture completion	12.2 (3.1)	13.7 (2.2)	0.021
WAIS III Digit symbol (coding)	8.6 (2.6)	10.5 (2.3)	0.003
Wechsler Test of Adult Reading (standard score)	90.0 (15.1)	100.4 (12.6)	0.002
WTAR-based predicted full WAIS III score	95.4 (8.8)	101.2 (7.9)	0.005
Delis–Kaplan Executive Function System (age scaled scores)			
D-KEFS-Verbal Fluency Test Cond 1	8.5 (3.2)	11.1 (3.4)	0.002
D-KEFS-Verbal Fluency Test Cond 2	9.3 (4.0)	11.0 (3.6)	0.073
D-KEFS-Colour-Word Interference Fluency Cond 1	8.1 (3.5)	10.3 (1.9)	0.004
D-KEFS-Colour-Word Interference Fluency Cond 2	8.8 (3.4)	10.3 (1.6)	0.033
D-KEFS-Colour-Word Interference Fluency Cond 3	9.0 (2.6)	10.2 (2.8)	0.073
D-KEFS-Colour-Word Interference Fluency Cond 4	8.3 (3.3)	10.2 (2.9)	0.012
Behavioural Assessment of Dysexecutive Syndrome			
Zoo Map Test (impairment score)	3.3 (0.8)	3.3 (0.8)	0.887
Rey Auditory Verbal Learning Test (No. of words recalled)			
RAVLT-Trial 1	6.5 (2.2)	6.8 (1.5)	0.536
RAVLT-Trial 2	9.4 (2.3)	9.9 (2.1)	0.294
RAVLT-Trial 3	10.8 (2.5)	11.2 (2.0)	0.424
RAVLT-Trial 4	11.3 (2.5)	12.1 (2.2)	0.128
RAVLT-Trial 5	12.3 (2.3)	12.9 (1.9)	0.198
RAVLT Distractor	5.0 (1.9)	6.1 (1.9)	0.016
RAVLT Recall	10.4 (3.1)	11.4 (2.5)	0.101
RAVLT Recognition	13.1 (2.5)	14.0 (1.3)	0.070
RAVLT Delayed Recall	10.4 (3.6)	11.1 (2.5)	0.314
Rey Complex Figure Test (raw scores)			
RCFT-Copy	33.8 (2.0)	34.1 (1.6)	0.497
RCFT-Immediate recall	20.6 (6.6)	21.7 (4.8)	0.389
RCFT-Delayed recall	20.7 (7.3)	22.7 (4.5)	0.179
Wechsler Memory Scale III (age scaled scores)			
WMS III Logical Memory 1—recall score	9.9 (3.4)	12.3 (1.9)	0.0002
WMS III Logical Memory 1—thematic score	10.4 (3.4)	12.0 (2.0)	0.006
WMS III Logical Memory 2—recall score	11.4 (3.0)	13.6 (2.2)	0.0001
WMS III Logical Memory 2—thematic score	10.6 (2.5)	12.7 (2.0)	0.0002
Trail making (time to completion)			
Time test A (s)	39.6 (24.3)	27.3 (9.2)	0.013
Time test B (s)	96.8 (64.8)	60.7 (14.9)	0.004
Beck Depression Inventory (2nd edition)	15.9 (8.4)	4.6 (5.9)	<0.000001

Table 4 Neuropsychological deficits sharing significant associations with the group differences in estimated WAIS-III full scale IQ

	Regression β-coefficient	*P*-value	Corrected group difference	*P*-value	Group difference significantly different from zero after controlling for IQ?
WAIS III Digit Span	0.54	0.001	−0.39	0.398	No
D-KEFS-Verbal Fluency Test Cond 1	0.40	0.02	−1.61	0.073	No
D-KEFS-Colour-Word Interference Fluency Cond 1	0.40	0.03	−1.21	0.106	No
D-KEFS-Colour-Word Interference Fluency Cond 2	0.63	0.0002	−0.17	0.796	No
Trail Making B time (s)	−0.41	0.02	20.72	0.147	No

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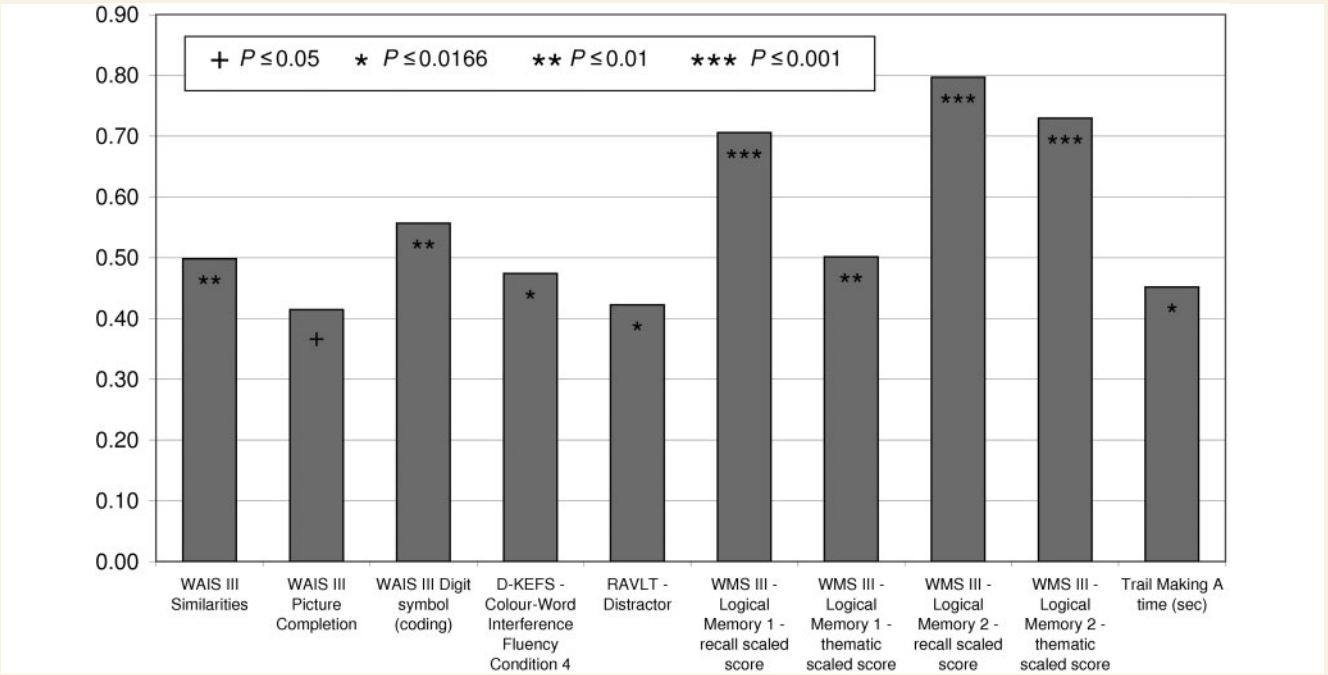


Figure 1 Effect sizes of all neuropsychological deficits without significant influence of estimated WAIS-III full-scale IQ or depression (sorted by task). The neuropsychological functions assessed by these measures include memory, complex attention and executive functions such as allocation of attentional resources and working memory, and speed of information processing. Mean effect size of the shown deficits was 0.56. Upon exclusion of the effect for WAIS-III Picture Completion, which was only marginally significant at $P<0.05$, the mean effect size was 0.57.

memory-guided sequences, the PCS group also showed marginal impairments with regard to poorer timing and rhythm keeping, with group disparities in ATI and IRI/IRI deviation approaching significance ($P<0.05$). The PCS group executed a smaller number of self-paced saccades, associated with a longer inter-saccadic interval of self-paced saccades. The PCS group had slower peak velocity of self-paced saccades and a strong trend towards longer saccade durations of self-paced saccades. In addition, there were multiple significant ($P<0.0166$) and marginally significant ($P<0.05$) group differences in the durations and time-to-peak velocity of anti-saccades and larger amplitude memory-guided saccades, with the PCS group being consistently worse on these measures (Table 6).

On OSP (Table 7), the PCS group had slower tracking velocity on 60°/s OSP and longer lag on random OSP, together with larger mean absolute errors on 60°/s OSP and random OSP. In addition, the PCS group had a marginally larger number of catch-up saccades on 40°/s OSP.

Analysis of covariance was used to explore whether the poorer eye movement performance was associated with the group differences in estimated WAIS-III FSIQ and depression (BDI II). Several group differences on self-paced saccades and OSP had some association with the group difference in depression. However, group differences remained on all these measures after correcting for the influence of depression (Table 8). There was only one oculomotor measure that was influenced by estimated IQ, namely the number of catch-up saccades in the 40°/s OSP task ($\beta=-0.47$, $P=0.01$). No group difference remained on this measure after correcting for the influence of IQ (corrected group difference 3.64, $P=0.322$). No other eye movement measures had significant associations with both estimated WAIS-III FSIQ and depression. The mean effect size of all group differences in eye movement functions unaffected by IQ and depression was 0.47 (Figs 2 and 3). Upon exclusion of eye movement measures with only marginally significant group differences ($P<0.05$), this mean effect size was 0.54.

Correlations of oculomotor function with health status

Due to the substantial number of correlations examined, only correlations at $P<0.01$ were considered significant in this analysis. Consistent with the view that there is a link between health status and abnormal brain function in PCS, we examined the correlations of health status with brain function as manifested in eye movements across the 'health spectrum' represented by the PCS and control groups. There were multiple correlations between eye movement function and health status (Table 9). All of these correlations occurred between health status and eye movement measures with significant and marginally significant group differences in performance.

Simulation of a clinical application of the present tests

This analysis simulated a clinical application of the applied tests by way of a 'checklist/diagnostic criterion' approach. The 15 variables

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Table 5 PCS versus non-PCS—saccades I—latencies, errors, number of saccades and accuracy

Measure	PCS group ($n = 36$) Mean (SD)	Non-PCS group ($n = 36$) Mean (SD)	*P*-value
Saccades—latency (ms)			
Reflexive saccades	175 (69)	157 (24)	0.126
Anti-saccades	275 (91)	266 (48)	0.593
Prosaccade errors (AS task)	174 (34)	159 (44)	0.127
Prosaccade correction (AS task)	120 (61)	110 (39)	0.443
Inter-saccadic interval of self-paced saccades	547 (270)	371 (102)	0.001
No. of self-paced saccades	49.5 (19.0)	62.4 (11.5)	0.0004
Saccades—directional errors (%)			
Anti-saccade-task	42.1 (19.5)	27.3 (23.4)	0.006
Memory-guided sequences	9.3 (11.4)	2.3 (4.1)	0.002
Saccades—accuracy			
Primary saccade gain (Gp)			
Reflexive saccades	0.95 (0.1)	0.96 (0.0)	0.737
Anti-saccades	1.34 (0.5)	1.14 (0.4)	0.108
Memory-guided sequences	0.92 (0.2)	0.88 (0.2)	0.480
Self-paced saccades	0.96 (0.1)	1.00 (0.1)	0.071
Gain final eye position (Gf)			
Reflexive saccades	1.00 (0.0)	1.00 (0.0)	0.701
Anti-saccades	1.26 (0.4)	1.02 (0.2)	0.004
Memory-guided sequences	1.18 (0.2)	1.13 (0.2)	0.131
Self-paced saccades	1.00 (0.1)	1.03 (0.1)	0.121
Position error (PE,%)			
Reflexive saccades	7.1 (3.9)	6.0 (2.8)	0.174
Anti-saccades	43.2 (32.2)	22.7 (10.0)	0.001
Memory-guided sequences	35.7 (12.9)	29.8 (11.6)	0.017
Memory-guided sequences			
Primary amplitude error	35.2 (10.1)	32.4 (9.9)	0.224
Final amplitude error	29.4 (11.0)	23.3 (8.9)	0.012
Memory-guided sequences			
ATI	1.14 (0.22)	1.04 (0.15)	0.043
IRI	0.01 (0.02)	0.00 (0.01)	0.031
IRI deviation (%)	22.7 (9.1)	19.1 (6.0)	0.038
Number of saccades			
Step 1	2.2 (0.7)	1.8 (0.8)	0.050
Step 2	2.4 (0.8)	2.1 (0.7)	0.092
Step 3	3.8 (0.9)	3.2 (0.6)	0.014

with the strongest effect sizes in the univariate comparisons in each modality (eye movement assessment or neuropsychological tests without WTAR—due to recruitment bias—and BDI II—due to the BDI being a mood-rating scale rather than a functional test) were dichotomized, assigning for each patient and measure a YES/NO-marker of abnormal performance based on scoring two standard deviations below the control mean. The number of abnormal measures falling below this threshold of functioning was then added for each participant (dichotomization score), followed by assessment of how many participants fell into the 'worst 40%' and 'worst 50%' of poor performance in each modality, and how this compared with the participants' symptom load. The number of 15 variables in each modality was chosen

Table 6 PCS versus non-PCS—saccades II—velocities and duration

Measure (in degrees)	PCS group ($n = 36$) Mean (SD)	Non-PCS group ($n = 36$) Mean (SD)	*P*-value
Saccades—velocity (deg/s)			
Reflexive saccades			
5	271 (45)	263 (29)	0.39
10	380 (59)	376 (48)	0.746
15	481 (65)	476 (55)	0.742
20	517 (71)	511 (50)	0.715
25	547 (69)	557 (62)	0.396
30	551 (117)	577 (57)	0.121
Anti-saccades			
5	325 (85)	285 (77)	0.096
15	339 (81)	309 (85)	0.184
Memory-guided saccades			
5	213 (72)	211 (61)	0.968
10	289 (75)	287 (47)	0.857
15	344 (80)	353 (72)	0.609
20	385 (78)	412 (70)	0.121
30	470 (90)	499 (77)	0.184
Self-paced saccades			
30	568 (94)	616 (82)	0.022
Saccades—duration (ms)			
Reflexive saccades			
5	61 (9)	61 (6)	0.985
10	74 (10)	72 (7)	0.499
15	83 (10)	82 (10)	0.749
20	92 (12)	93 (18)	0.829
25	101 (21)	101 (16)	0.927
30	108 (26)	118 (33)	0.171
Anti-saccades			
5	110 (43)	84 (21)	0.002
15	105 (36)	89 (25)	0.035
Memory-guided saccades			
5	64 (11)	65 (10)	0.508
10	81 (19)	77 (10)	0.372
15	104 (32)	88 (16)	0.009
20	110 (32)	99 (16)	0.05
30	154 (54)	130 (27)	0.023
Self-paced saccades			
30	141 (37)	124 (16)	0.018
Saccades—time-to-peak velocity (ms)			
Reflexive saccades			
5	24 (2)	25 (2)	0.477
10	29 (2)	29 (2)	0.556
15	32 (3)	32 (2)	0.714
20	35 (3)	35 (5)	0.964
25	36 (5)	35 (3)	0.484
30	37 (8)	38 (7)	0.527
Anti-saccades			
5	36 (10)	31 (8)	0.017
15	35 (9)	31 (8)	0.099
Memory-guided saccades			
5	25 (4)	25 (3)	0.955
10	30 (5)	28 (3)	0.055
15	34 (8)	32 (7)	0.104
20	36 (10)	36 (7)	0.676
30	46 (18)	40 (7)	0.109
Self-paced saccades			
30	45 (12)	40 (5)	0.023

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to preserve detection sensitivity whilst allowing for some poor performance in the non-PCS group, and to promote a healthy distribution of the dichotomization scores under prevention of floor/ceiling effects.

The scoring range of the dichotomization scores in the PCS group differed slightly between the two measure modalities. Both modalities had minima of zero but the maxima differed, with a worst score of 10 for the eye movement assessment and 13 for the neuropsychological tests. For the subsequent evaluation, the observed maxima were treated as maximal obtainable scores. Hence, participants in the 'worst 40%' of eye movement performance had to have dichotomization/abnormality scores of 6 or higher (i.e. a patient had to have abnormal eye movement function on 6 or more of the assessed eye movement measures). For the neuropsychological tests, a score of 8 or higher was required. The equivalent scores for determining the 'worst 50%' for eye movement performance and neuropsychological tests were '5 or higher' and '7 or higher', respectively.

Eight PCS participants were within the 'worst 40%' regarding eye movement function (Table 10). Only five met this criterion for the neuropsychological tests. There was an overlap, with four participants being amongst the worst 40% for both the eye movements and the neuropsychological testing. However, eye movements were slightly better in 'detecting' abnormal brain function in the participants with the highest symptom load on the RPSQ, detecting three cases who had not been 'identified' as having markedly impaired brain function by neuropsychological testing, including the patient with the highest symptom load. Most of the participants detected as markedly impaired by either eye movement measures or neuropsychological testing were amongst the 'worst 40%' in terms of symptom severity on the RPSQ (Table 10).

Relaxing the threshold to a 'worst 50%' criterion did not change the 'detection sensitivity' for the neuropsychological tests but resulted in an additional three 'detections' on the eye movement side (one in the worst symptom range and two in the less severe PCS spectrum). Relaxing the classification threshold for poor performance further was not feasible as the subsequent scoring range would have overlapped with that of the non-PCS controls. The range of the controls' dichotomization scores for the neuropsychological tests was 0–2 (i.e. there were controls who had abnormal performance in two neuropsychological measure categories based on the '2 SDs below control standard'), with the equivalent range of the controls' eye movement function being 0–4.

The dichotomization scores of the PCS group correlated with several health status measures of symptom load (RPSQ), activities of daily living (AOL) (RHIFQ) and mental health (SF-36) (Table 11), the eye movements having stronger correlations with symptom load and activities of daily living whilst neuropsychological scores had slightly better correlations with measures of mental health (Table 11). Inter-modality correlations of the eye movement and neuropsychological dichotomization scores was strong ($R = 0.71$, $P < 0.0001$).

The group comparisons had shown poorer results of the PCS group on nine saccadic parameters that are beyond conscious control, indicating poorer subcortical brain function (Fig. 3). This raised the question of whether this kind of subcortical dysfunction was present in many PCS participants. We determined on how many of these nine measures our participants performed at least two SDs below the control mean, calculating a 'subcortical impairment index' by adding the number of abnormal subcortical measures falling below this threshold of functioning for each participant. In the PCS group, the scores of this 'subcortical index' ranged between 1 and 7. In contrast, the subcortical index score in the non-PCS group was 0 in 30 participants, 1 in

Table 7 PCS versus non-PCS patients—OSP

Measure	PCS group ($n = 36$) Mean (SD)	Non-PCS group ($n = 36$) Mean (SD)	*P*-value
OSP			
40°/s			
Average peak velocity	34.8 (3.5)	36.3 (2.5)	0.061
Lag (ms)	6.5 (25.0)	3.2 (14.7)	0.454
Mean absolute error (deg)	1.7 (0.7)	1.5 (0.6)	0.512
Number of catch-up saccades	60.4 (16.4)	53.3 (17.0)	0.037
60°/s			
Average peak velocity	48.6 (5.5)	52.3 (3.9)	0.005
Lag (ms)	30.3 (26.0)	29.2 (11.7)	0.822
Mean absolute error (deg)	2.6 (*0.9*)	2.0 (*0.7*)	0.011
Number of catch-up saccades	80.6 (21.1)	74.5 (19.1)	0.189
Random			
Average peak velocity	26.6 (7.3)	29.6 (5.3)	0.073
Lag (ms)	51.5 (25.0)	33.5 (15.9)	0.001
Mean absolute error (deg)	2.7 (*0.9*)	2.0 (*0.4*)	0.0006
Number of catch-up saccades	152.8 (38.9)	156.6 (27.3)	0.624

Table 8 Eye movement deficits sharing significant associations with the group differences in depression

	Regression β-coefficient	*P*-value	Corrected group difference	*P*-value	Group difference significantly different from zero after controlling for depression?
Number of self-paced saccades	0.39	0.02	−22.6	0.0001	Yes
Inter-saccadic interval self-paced saccades	−0.38	0.03	309.4	0.0002	Yes
Velocity self-paced saccades	0.35	0.04	−95.4	0.005	Yes
OSP 40°—number of saccades	−0.38	0.03	17.0	0.003	Yes
OSP random—lag	−0.41	0.02	33.6	0.0001	Yes

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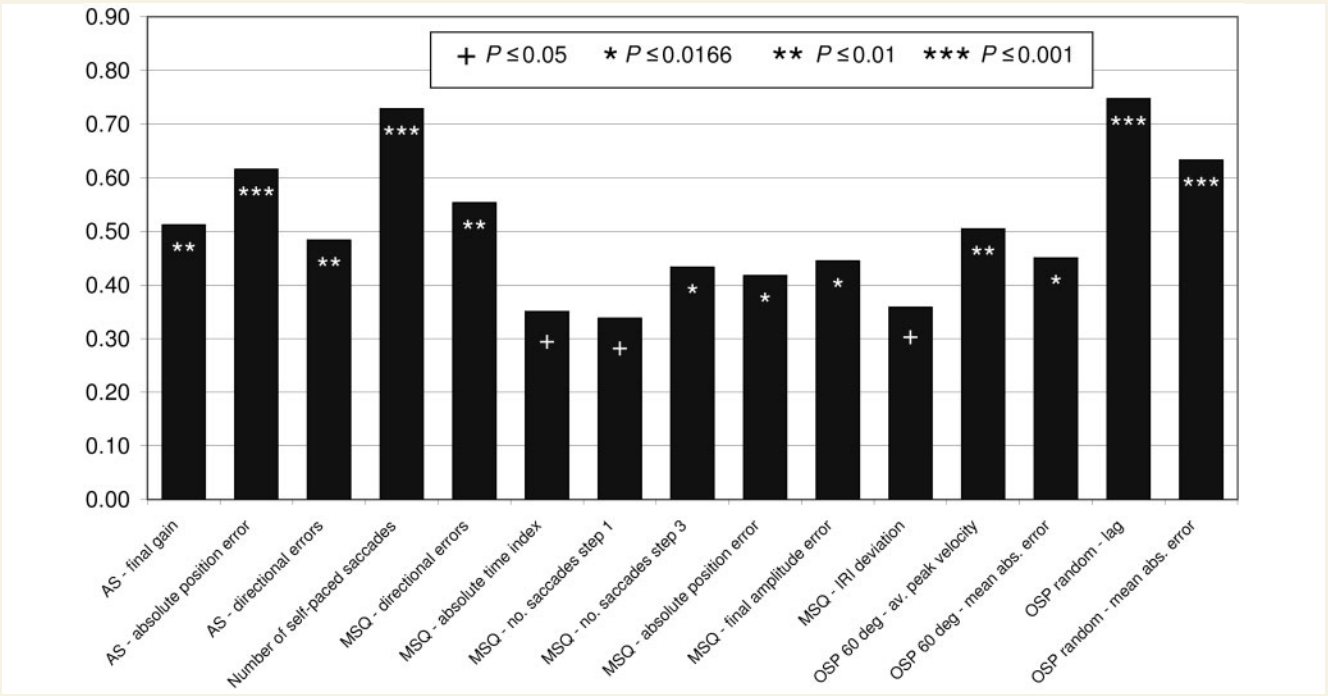


Figure 2 Effect sizes of deficits in eye movement functions under conscious (saccadic tasks) and semi-conscious control (OSP) (measures sorted by task). For number of self-paced saccades and the lag of random OSP, the adjusted effect sizes after controlling for depression are shown. Mean effect size of the deficits shown in Figs 2 and 3 was 0.47. Upon exclusion of eye movement measures with only marginally significant group differences ($P < 0.05$), this mean effect size was 0.54. AS = anti-saccades; MSQ = memory-guided sequences; OSP = oculomotor smooth pursuit.

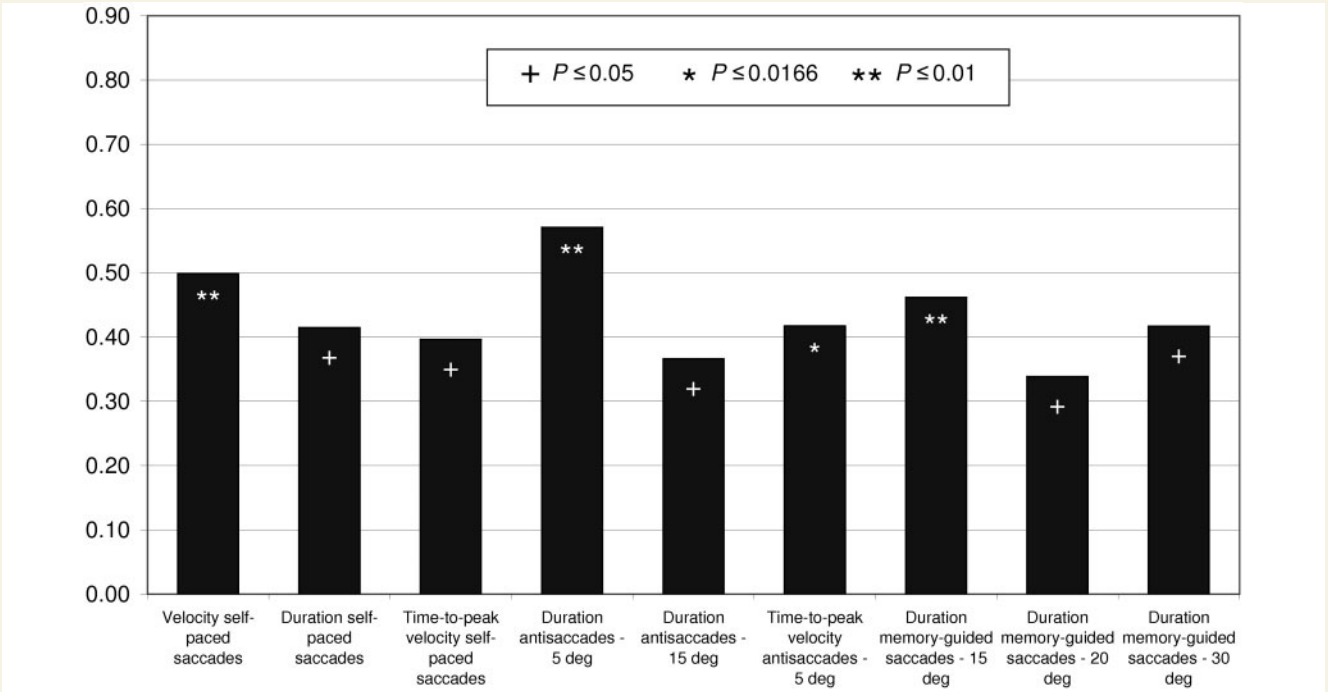


Figure 3 Effect sizes of deficits in eye movement functions beyond conscious control (saccadic tasks) (measures sorted by task). For velocity of self-paced saccades, the adjusted effect size after controlling for depression is shown.

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Table 9 Correlations of eye movement function with measures of health status over all subjects

Health status	Correlating eye movement measure	Pearson *R*	*P*-value
RPSQ total	No. of self-paced saccades	−0.41	0.001
	Self-paced saccades—inter-saccadic interval	0.45	<0.001
	Self-paced saccades—duration	0.31	0.001
	Memory-guided sequences—no. of directional errors	0.44	0.003
	Memory-guided sequences—ATI	0.35	0.005
	Memory-guided sequences—final amplitude error	0.31	0.005
	60°/s sinusoidal OSP—mean abs. error	0.34	0.002
	Random OSP—lag	0.41	0.001
	Random OSP—mean absolute error	0.44	<0.001
	Memory-guided sequences —duration 15° saccades	0.32	0.003
	Memory-guided sequences —duration 20° saccades	0.36	<0.001
	Memory-guided sequences — duration 30° saccades	0.31	0.002
	Memory-guided sequences —time-to-peak velocity 30°	0.35	0.002
RHIFQ total	Anti-saccades—final saccade gain	0.36	0.001
	Anti-saccades—absolute position error	0.34	0.002
	No. of self-paced saccades	−0.46	<0.001
	Self-paced saccades—inter-saccadic interval	0.49	<0.001
	Self-paced saccades—velocity	−0.35	0.003
	Self-paced saccades—duration	0.37	0.002
	Memory-guided sequences —no. of directional errors	0.39	0.001
	Memory-guided sequences —ATI	0.36	0.002
	Memory-guided sequences—no. of sacc. step 3	0.33	0.003
	Memory-guided sequences—absolute positon error	0.35	0.002
	Memory-guided sequences—final amplitude error	0.38	0.001
	60°/s sinusoidal OSP—mean abs. error	0.40	<0.001
	Random OSP—lag	0.47	<0.001
	Random OSP—mean absolute error	0.51	<0.001
	Anti-saccades—duration 5° saccades	0.32	0.005
	Memory-guided sequences—duration 20° saccades	0.33	0.001
	Memory-guided sequences—duration 30° saccades	0.32	0.002
SF-36 physical summary	Memory-guided sequences—no. of directional errors	−0.36	0.002
	Anti-saccades—duration 15° saccades	−0.34	0.003
SF-36 mental summary	No. of self-paced saccades	0.41	0.001
	Self-paced saccades—inter-saccadic interval	−0.40	<0.001
	Self-paced saccades—duration	−0.35	0.005
	Memory-guided sequences—ATI	−0.32	0.008
	60°/s sinusoidal OSP—mean abs. error	−0.43	<0.001
	Random OSP—lag	−0.36	0.004
	Random OSP—mean absolute error	−0.38	0.001
	Memory-guided sequences—duration 20° saccades	−0.32	0.007
	Memory-guided sequences—duration 30° saccades	−0.36	0.002
	Memory-guided sequences—time-to-peak velocity 30°	−0.37	0.002

3 participants, 2 in 2 participants and 5 in 1 participant. We then examined how many PCS participants had a 'subcortical index' of 4 or higher, this being seen as sufficient to suggest an abnormal level of subcortical functionality whilst excluding 97% of the scores in the non-PCS control group. The results showed that poor subcortical functionality was most prevalent in the group of PCS participants with the highest symptom load on the RPSQ (Table 10). Nine PCS participants had a subcortical index of $\geqslant 4$, and seven of these were in the worst 40% in terms of symptom severity on the RPSQ (Table 10). Subcortical functionality correlated better with health status measures than the 'overall' eye movement dichotomization scores (Table 11).

Discussion

This is the first study to have examined eye movement function in mCHI patients presenting with PCS. Our results indicate that eye movement function is impaired in PCS, the deficits being unrelated to the influence of depression or estimated intellectual ability, which affected some of the neuropsychological tests. The majority of eye movement deficits in the PCS group were found on measures relating to motor functions executed under both conscious and semi-conscious control (directional errors; poorer visuospatial accuracy; more saccades and marginally poorer timing and rhythm keeping in memory-guided sequences; smaller

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Table 10 PCS-group—dichotomization analysis

Patients—ranked by RPSQ total	RPSQ total (max. of 64)	RHIFQ total (max. of 40)	SF-36 physical summary (normal = 50)	SF-36 mental summary (normal = 50)	Number of neuropsychological measures below abnormal threshold	Number of eye movement measures below abnormal threshold	Within 'worst 40%' of bad neuropsychological performance	Within 'worst 40%' of bad eye movement performance	Within 'worst 50%' of bad neuropsychological performance	Within 'worst 50%' of bad eye movement performance
PCS 1[a]	51	27	44	17	1	6		YES		YES
PCS 2[a]	47	16	31	30	10	8	YES	YES	YES	YES
PCS 3[a]	42	28	37	37	5	3				
PCS 4[a]	40	31	52	13	5	5				YES
PCS 5	38	21	29	42	1	2				
PCS 6	38	19	41	31	0	2				
PCS 7	38	23	56	19	13	9	YES	YES	YES	YES
PCS 8[a]	35	29	52	40	3	9		YES		YES
PCS 9	34	16	48	34	3	2				
PCS 10	32	19	41	34	0	1				
PCS 11	31	28	53	15	9	10	YES	YES	YES	YES
PCS 12[a]	30	20	50	41	4	8		YES		YES
PCS 13	29	21	40	46	11	8	YES	YES	YES	YES
PCS 14[a]	28	21	45	45	0	3				
PCS 15	28	12	45	54	0	1	'Worst 40%' threshold for symptom severity on the RPSQ			
PCS 16	27	19	59	25	1	3				
PCS 17	27	23	36	34	1	4				
PCS 18	26	20	37	29	1	0				
PCS 19	25	17	42	22	9	3	YES		YES	
PCS 20	25	11	52	34	1	3				
PCS 21[a]	25	29	36	17	2	3				
PCS 22[a]	25	6	49	29	3	2				
PCS 23	24	4	58	35	1	0				
PCS 24	24	12	47	29	0	2				
PCS 25	21	25	53	51	3	3				
PCS 26	17	13	52	42	0	0				
PCS 27	16	5	51	51	0	1				
PCS 28	15	19	48	41	1	5				YES
PCS 29	15	8	49	45	0	2				
PCS 30	15	7	44	42	0	4				
PCS 31	15	2	59	42	0	0				
PCS 32	14	8	44	45	3	5				YES
PCS 33	14	9	52	42	6	6		YES		YES
PCS 34	13	9	50	55	5	2				
PCS 35	10	9	47	55	0	2				
PCS 36	9	16	38	46	1	2				

a Four or more of the nine 'subcortical' saccadic measures with group differences (velocities, durations, time-to-peak velocity) were below 2 SDs of control mean in that participant.

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Table 11 Dichotomization analysis, PCS group correlations between performance scores and health status

	Dichotomization score neuropsychological tests (Pearson *R*)	*P*-value	Dichotomization score eye movement tests (Pearson *R*)	*P*-value	Eye movement subcortical index (Pearson R)	*P*-value
Total on the RPSQ	0.34	0.04	0.39	0.02	0.34	0.04
Total on the RHIFQ	0.32	0.06	0.50	0.002	0.28	0.10
SF-36 health survey—scales						
Physical function	−0.13	0.45	−0.08	0.64	−0.05	0.75
Role-physical	−0.26	0.13	−0.28	0.10	−0.07	0.69
Bodily pain	0.03	0.85	0.04	0.82	−0.31	0.07
General health	−0.15	0.39	−0.02	0.91	−0.36	0.03
Vitality	−0.22	0.20	−0.10	0.55	−0.20	0.25
Social function	−0.24	0.16	−0.30	0.08	−0.38	0.02
Role-emotional	−0.23	0.18	−0.26	0.12	−0.17	0.32
Mental health	−0.38	0.02	−0.30	0.08	−0.38	0.02
SF-36 physical summary	−0.02	0.91	0.02	0.90	−0.15	0.39
SF-36 mental summary	−0.34	0.04	−0.32	0.05	−0.34	0.04

number of self-paced saccades; deficits in OSP). Importantly, the PCS group also had poorer performance on several eye movement functions that are beyond conscious control and indicative of subcortical brain function (slowed velocity of self-paced saccades and indications of longer saccade durations of self-paced saccades, anti-saccades and larger amplitude memory-guided saccades). Cognitive functions likely affected in the PCS group based on the eye movement deficits include decision making, response inhibition, short-term spatial memory, motor-sequence programming and execution, visuospatial information processing and integration and visual attention (Pierrot-Deseilligny *et al*., 2004; Leigh and Zee, 2006). These results indicate that brain function in the PCS group had not returned to normal and contrasted that seen in patients with good recovery. There were significant correlations between health status as assessed by RPSQ, RHIFQ and SF-36 and the oculomotor measures with between-group differences, including several eye movement measures with only marginally significant ($P<0.05$) group differences. The presence of these correlations suggests that even the weaker effects amongst the observed oculomotor group differences can be considered relevant in establishing the oculomotor impairment profile of PCS. The composition of the group differences in oculomotor function shows that the impairment of the PCS group was task related (anti-saccades, memory-guided sequences, self-pacing, OSP, with no impairments in reflexive saccades), with specific eye movement parameters (accuracy, response errors, subconscious saccadic parameters, OSP tracking ability) showing impairments across several eye movement paradigms. The nature of these results in combination with the finding of significant correlations between health status as assessed by RPSQ, RHIFQ and SF-36 and the eye movement measures with group differences would suggest that the PCS effects we are detecting are genuine and not a consequence of type I statistical errors.

The results of the neuropsychological assessment were consistent with the findings of previous studies. Previous research has shown that the ability of neuropsychological testing to accurately detect cognitive decrements associated with a mCHI diminishes with the passage of time (Binder *et al*., 1997; Schretlen and Shapiro, 2003; Iverson, 2005). This limited ability of neuropsychological testing to document ongoing impairment in brain function in mCHI was also reflected in our results. Out of all neuropsychological test measures applied, group differences at $P<0.05$ emerged on only 10 of these measures after controlling for estimated IQ, and the dichotomization analysis documented markedly abnormal neuropsychological function in only 5 of 36 PCS patients. However, the presence of some neuropsychological deficits in the PCS group is consistent with the markedly poor recovery status of this group, which was sufficiently severe to meet a symptom profile as prescribed by the WHO-based criteria for PCS. As recent imaging studies indicate an emerging link between (white matter) lesions and both persistent symptom status and poorer cognitive performance (Hofman *et al*., 2002; Salmond *et al*., 2006; Bazarian *et al*., 2007; Chen *et al*., 2008; Lipton *et al*., 2008; Miles *et al*., 2008; Niogi *et al*., 2008), it is likely that the presence of, albeit relatively few, neuropsychological deficits in the PCS group is a manifestation of this group's poor recovery status even at ~140 days post-injury.

A problem intrinsic to clinical research is the question of whether the studied patient sample is representative. Based on the demographic parameters, the current sample compares well with the patient populations presenting with persistent post-concussional complaints to Concussion Clinics in New Zealand (Snell and Surgenor, 2006; Alexander *et al*., 2007). With regard to both the endorsement of symptoms and neuropsychological performance, we consider the present patient sample representative of the majority of PCS patients (Carroll *et al*., 2004; Iverson, 2005). Due to the application of WHO-based criteria for PCS, and the subsequent requirements of a relatively wide spectrum of symptomatic complaints, one might argue that our current PCS sample was biased towards the more severe side of the PCS spectrum. However, the current PCS sample covers a comprehensive range of case severities (Table 10), representative of PCS populations seen in an 'every-day' context. Similarly, the present contrast between extensive symptom endorsement but limited neuropsychological abnormalities is a phenomenon frequently encountered by clinicians and rehabilitationists in the context of PCS and falls in

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line with a body of evidence suggesting a limited sensitivity of neuropsychological testing in detecting abnormalities in brain function several months after mCHI (Binder *et al*., 1997; Schretlen and Shapiro, 2003; Iverson, 2005). A particular strength of the current study is that funding for healthcare services and injury-related costs was uniform across subjects and that the studied groups were free of issues relating to litigation or monetary compensation due to the nature of the New Zealand healthcare system. In turn, this contributed to avoiding result distortion by issues relating to litigation whilst also controlling for factors such as drug abuse, neurological disorders or psychiatric conditions.

Based on the composition of group differences in eye movement function, it is unlikely that the poorer performance of the PCS group was due to a lack of effort or intentionally poor performance. This conclusion is supported by the lack of group differences in saccadic latencies and by the absence of significant associations between poorer eye movement function and depression for most measures. Whilst we observed a number of eye movement deficits that may be vulnerable to lack of effort or deliberately poor performance (e.g. directional errors on anti-saccades and memory-guided sequences, number of self-paced saccades, spatial accuracy), the PCS group also exhibited impairments on several measures that are beyond conscious control (saccadic velocity of self-paced saccades and saccade durations) (Enderle, 2002; Leigh and Zee, 2006). All participants had volunteered for the study, were happy to attend, and were aware that the study assessment was not part of any clinical evaluation. Motivational factors were also clinically assessed for all participants as part of the neuropsychological assessment. This assessment confirmed that subject compliance and test effort on the neuropsychological tests was sufficient for study inclusion. Based on these factors, we consider it unlikely that motivational factors are responsible for the present results.

Both groups were sufficiently matched for injury severity. Based on the range of GCS scores and the presence/duration of PTA and LOC in our groups, the mean degree of injury severity in the non-PCS group was similar, if not slightly more severe, to that of the PCS group. Hence, the group disparities in oculomotor and neuropsychological function are unlikely to be due to different trauma severities.

On average, the controls in this study were assessed 23 days later than the participants in the PCS group. This difference was significant and one might argue that the participants in the PCS group may have performed better had they been assessed later due to having had more time to achieve recovery of brain function. However, the known recovery timeline of oculomotor function in the first 6 months after mCHI shows that this recovery should be complete at this point and that any improvement that still may occur between ~140 and 160 days post-injury is, at most, very minimal (Heitger *et al*., 2006). Also, all controls had undergone the same eye movement tests once before within the first 10 days post-injury, due to their involvement in a parallel study examining the relationship between early motor function and recovery after mCHI, which raises the question of practice effects. However, the findings of repeated assessment of healthy controls on the current eye movement tasks at three monthly intervals over the course of a year (Heitger *et al*., 2006) do not support the influence of practice effects.

An important point is the marked group disparity between scores on the BDI, as there is evidence that depression itself is associated with abnormalities in saccadic and OSP function. Patients with major depressive disorder have been found to show impairment of eye movement function, including more directional errors on anti-saccades, longer duration and higher variability of anti-saccade latencies, longer reflexive latencies, reduced velocity of self-paced saccades, prolonged saccade durations in anti-saccades and memory-guided saccades, and impairments of OSP (Malaspina *et al*., 1994; Flechtner *et al*., 1997; Sweeney *et al*., 1998; Mahlberg *et al*., 2001; Crevits *et al*., 2005; Jazbec *et al*., 2005; Winograd-Gurvich *et al*., 2006). Several of these deficits were also observed in our PCS group. However, other key deficits, such as prolonged latencies on reflexive saccades and anti-saccades, were absent and there was no association between the group differences in depression and eye movement function for most oculomotor measures. The few eye movement deficits sharing associations with the group difference in depression continued to show group differences after controlling for this influence of depression. Hence, the eye movement disparities between the PCS and non-PCS groups cannot be attributed to depression.

Another relevant issue in the discussion of the current findings is the question of whether any of the observed group differences may have been influenced by factors relating to injury-related anxiety disorders, including post-traumatic stress disorder (PTSD), which can occur concomitantly with PCS, manifesting symptom spectra similar to those used to define PCS. Based on the clinical screening process during recruitment for this study, we can largely exclude an influence of PTSD in the PCS group. All PCS participants were seen and assessed by a neuropsychiatrist (A.D. MacLeod) before study inclusion as part of their clinical assessment at the Concussion Clinic and none met the criteria for a diagnosis of PTSD as documented by their clinical reports. In addition to these considerations, the current literature on eye movement control in psychological disorders does not support the conclusion that the eye movement deficits observed in the PCS group were due to a systematic influence of anxiety disorders. Studies examining eye movement control in generalized anxiety disorder and obsessive–compulsive disorder indicate that the adverse impact of such entities on the control of saccadic and OSP eye movements in standard test paradigms is small. The associated eye movement performance does not match the deficits observed in the current PCS group and there is no evidence that anxiety disorders cause systematic deficits on measures assessed in the present study, such as directional errors in saccadic tasks, saccade initiation and reaction times, motor learning, saccadic accuracy or duration or velocity of saccades (Nickoloff *et al*., 1991; Sweeney *et al*., 1992; Farber *et al*., 1997; Maruff *et al*., 1999; Smyrnis *et al*., 2003, 2004; Lencer *et al*., 2004; Jazbec *et al*., 2005; Spengler *et al*., 2006). There is some evidence of a systematic influence of anxiety disorders on OSP but the reported deficits occur on measures not applied in the current study, such as number of OSP intrusions or number of anticipatory saccades (Sweeney *et al*., 1992; Spengler *et al*., 2006), whereas measures

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found to be impaired in the PCS group have been found unaffected in anxiety disorders, such as tracking velocity (Nickoloff *et al*., 1991; Lencer *et al*., 2004; Spengler *et al*., 2006). Beyond this research on eye movement control in general anxiety disorders, there is little evidence of eye movement deficits in post-traumatic stress disorder. Despite a considerable research interest on the use of eye movements as part of desensitization processing therapy in post-traumatic stress disorder, no study has, to our knowledge, measured saccadic performance parameters specifically in PTSD, and only one study has examined OSP in PTSD (Cerbone *et al*., 2003), reporting a decreased ability to maintain OSP in PTSD with secondary psychotic symptoms, this being consistent with evidence of OSP deficits seen in other anxiety disorders. Based on the factors outlined above, the eye movement abnormalities in our PCS group likely relate specifically to the presence of PCS, manifesting an oculomotor impairment profile that is distinguishable from other disorders.

Other factors relevant in determining poorer outcome after mCHI are age and gender. However, both of these factors were closely controlled for in this study and, therefore, can be excluded as confounding factors in the results. Eye movement function as measured in this study is not affected by gender. Similarly, age decrements in eye movement performance are small compared with neuropsychological testing. Whilst there is an influence of age and a subsequent change in the level of oculomotor performance over time, the most 'dynamic' phases of this change occur at the very beginning and end of a normal life span with eye movement performance being relatively stable between the age of 16 and 70 years (Munoz *et al*., 1998; Shafiq-Antonacci *et al*., 1999; Knox *et al*., 2005; Irving *et al*., 2006; Luna *et al*., 2008).

The present neuropsychological findings indicate several impaired cognitive functions in the PCS group, such as memory, complex attention and executive functions such as allocation of attentional resources and working memory, and speed of information processing. There may have been a contribution of these factors to the poorer eye movement control in the PCS group as the eye movement tests require conscious and controlled responses with sizable cognitive load (Pierrot-Deseilligny *et al*., 2004; Barnes, 2008; Gooding and Basso, 2008; Hutton, 2008). Impairments on several saccadic parameters in the PCS group suggest poorer function of the PCS group with regard to response inhibition, short-term memory, aspects of attention and decision making under time pressure. In particular, the poorer results of the PCS group on directional errors in the anti-saccade task suggest poorer function with regard to response inhibition. The inhibition of reflexive responses (erroneous prosaccades towards the anti-saccade stimulus) is a prerequisite to performing well on this task. Inability to suppress these erroneous responses will result in higher numbers of directional errors. In addition, there is a complex contribution of attentional factors to the anti-saccade task and attentional deficits will result in poorer performance of this task (Gooding and Basso, 2008; Hutton, 2008). Deficits in the anti-saccade task in non-head injury populations have been assigned to impairments in attentional focus, impaired inhibitory control, impairments in the implementation of inhibition, working memory impairments, goal neglect and an inability to generate a voluntary action (Gooding and Basso, 2008; Hutton, 2008). The normal saccadic reaction times in the PCS group indicate that ability to generate action and the factors relating to the deployment of attention were not affected in the PCS group. The poorer result of the PCS group on number of self-paced saccades conveys the impression that the PCS group had more difficulty in quickly disengaging attention and switching visual attention under time pressure. This interpretation is consistent with previous eye movement studies in patients with mCHI suggesting that, amongst all aspects of visual attention, disengagement of attention is most vulnerable to the adverse functional impact of mild head trauma (Drew *et al*., 2007). Based on the present findings, impairment of working memory in the PCS group, an important facet in cognitive factors contributing to both the anti-saccades and memory-guided sequences cannot be ruled out. The higher number of saccades made by the PCS group in the memory-guided sequences together with a higher number of directional errors, poorer visuospatial accuracy and marginally poorer timing/rhythm keeping indicate that the PCS group clearly perceived the memory-guided sequence task as much more of a challenge in terms of maintaining correct sequence order and delivering (perceived) temporal and visuospatial accuracy. In addition to problems in planning and accurately executing complex motor programmes, this may also indicate problems with (short-term) spatial memory and difficulty in accurately memorizing a motor program. However, cognitive load on the eye movement tests is smaller than in many neuropsychological tests, the task complexity being smaller and task durations shorter (i.e. 60–180 s rather than 15–30 min common for many neuropsychological tests). It is possible but unlikely that neuropsychological or cognitive factors can account for the entire difference in eye movement function between the groups, implying that the observed eye movement deficits were likely related to poorer functionality of the cerebral structures for eye movement control.

There is considerable functional overlap in the activation of specific structures in different eye movement tasks and, hence, the assessment of eye movement function can generally not be used to localize neural injury or brain lesions in individuals with non-severe head trauma. However, the composition of group-level oculomotor deficits suggests poorer functionality of some cerebral structures for eye movement control in the PCS group. The higher number of directional errors of the PCS group in the anti-saccade task suggests suboptimal function in prefrontal cortical areas, in particular the dorsolateral prefrontal cortex (Walker *et al*., 1998; Pierrot-Deseilligny *et al*., 2003*a*; Leigh and Zee, 2006), an interpretation consistent with the results of the neuropsychological testing. The smaller number of self-paced saccades and prolonged inter-saccadic latency of self-paced saccades in the PCS group supports the interpretation of poorer prefrontal function (Williams *et al*., 1997). The slower peak velocity and longer duration of self-paced saccades, and the longer durations of anti-saccades and larger amplitude saccades in memory-guided sequences raises questions about problems in subcortical processing in the PCS group (Leigh and Zee, 2006). However, the group differences in these subconscious measures occurred only in tasks with endogenously generated eye movements whilst reflexive saccades were completely normal. This suggests that the origin

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of poorer performance on these paradigms was not simply a poorer subcortical functionality, but disturbances/imbalances in information transfer between cortical and subcortical areas, potentially leading to abnormal pattern activation in structures such as the superior colliculus (Johnston and Everling, 2008). The absence of any group disparities on saccadic latencies and the similar numbers of catch-up saccades in the OSP tasks suggest comparable functionality of the frontal eye fields (Pierrot-Deseilligny *et al*., 2004; Leigh and Zee, 2006; Müri and Nyffeler, 2008). However, the combination of poorer spatial accuracy of the PCS group on anti-saccades and sequences of memory-guided saccades, poorer results on timing and rhythm keeping and higher number of saccades and directional errors made in memory-guided sequences, may be indicative of impaired functionality of the other frontal areas such as the supplementary eye fields (Gaymard *et al*., 1990; Müri *et al*., 1994, 1995; Sweeney *et al*., 1996; Everling *et al*., 1997, 1998; Schlag-Rey *et al*., 1997; Pierrot-Deseilligny *et al*., 2004; Leigh and Zee, 2006; Müri and Nyffeler, 2008). All group differences in saccadic accuracy occurred in tasks with endogenously generated eye movements, suggestive of problems in motor programming/efficiency of internal motor models (Hutton, 2008). Suboptimal function in parietal cortical areas such as the posterior parietal cortex cannot be ruled out. The posterior parietal cortex is the cortical substrate for visuospatial attention, spatial transformation, positional coding and integration of primary visuosensory information for the accuracy of sequences of memory-guided saccades (Heide *et al*., 2001; van Donkelaar and Müri, 2002; Pierrot-Deseilligny *et al*., 2003b; Leigh and Zee, 2006) and further participates in generating a neural representation of the anti-saccade stimulus in the hemifield ipsilateral to the stimulus before saccade generation (Everling *et al*., 1998; Leigh and Zee, 2006). The interpretation of impaired function in visuospatial parietal areas is, however, countered by the finding of similar latency of reflexive saccades in both groups, suggesting comparable function of the parietal eye fields, a structure relevant for the initiation of reflexive visually guided saccades (Pierrot-Deseilligny *et al*., 2004; Leigh and Zee, 2006; Müri and Nyffeler, 2008). The poorer performance of the PCS group on several measures of OSP supports the interpretation of suboptimal function in cortical and subcortical areas and/or the cerebellum and its brainstem connections (Thier and Ilg, 2005; Sharpe, 2008).

The poorer performance of the PCS group on functions beyond conscious control in several types of saccades and the finding of multiple correlations between the 'subcortical' dichotomization index and measures of health status imply that the 'gradient' of dysfunction in the PCS group reached beyond the grey-and-white matter junction into subcortical areas. There is considerable evidence that mCHI adversely affects predominantly frontal, temporal and parietal cerebral areas, while damage to deeper brain areas is progressively smaller and less frequent (Gray *et al*., 1992; Jacobs *et al*., 1996; Kant *et al*., 1997; Otte *et al*., 1997; Bicik *et al*., 1998; Abu-Judeh *et al*., 1999; Hofman *et al*., 2002; Chen *et al*., 2003; Bigler, 2008). Our findings suggest a greater adverse impact on subcortical brain function in the PCS group than expected after mCHI, with PCS cases in the more severe symptom spectrum showing the most impairment in this area. These findings support previous notions that PCS after mCHI is not a purely psychological entity but also has a biological substrate (Jacobs *et al*., 1996; McAllister *et al*., 1999; Radanov *et al*., 1999; Gaetz and Weinberg, 2000; Hofman *et al*., 2002; Duff, 2004; Bigler, 2008).

In examining the question of whether it would be useful to routinely supplement patient assessment with eye movement testing, it has to be acknowledged that the eye movement findings were not as strong as anticipated. The mean eye movement effect size was slightly smaller than observed for the neuropsychological testing. The dichotomization analyses also indicated that the transposition of the group-level effects to an individual level is likely associated with variability and that the magnitude of oculomotor impairment may vary between individuals with similar symptom load. Whilst some patients, particularly in the more severe PCS spectrum, may show marked impairment on multiple eye movement measures, impairment of eye movement function in other mCHI patients with PCS may still be present but more subtle (i.e. falling above the '2 SD below control mean' threshold applied here). Despite the slightly better ability of eye movements to document markedly abnormal brain function amongst PCS participants with the highest symptom load, and the better correlations of poor oculomotor function with symptom load and problems on activities of daily living, the 'eyes' were not substantially better, and 66% of PCS participants were not identified as having markedly impaired brain function by either eye movement assessment or neuropsychological testing. The potential drawback then is that poor eye movement function may reflect incomplete recovery of brain function in individual cases of PCS but the absence of marked oculomotor impairment may not necessarily indicate a good recovery or an absence of PCS. However, due to its relatively short test duration, its ability to sample subcortical/subconscious brain function, and its independence from factors such as depression, intellectual ability, socioeconomic tier, level of education and skill-level of everyday activity/occupation, eye movement assessment may still be a useful screening tool to identify suboptimal brain function in large high-risk groups in the context of mCHI, such as military personnel with non-severe head trauma (or exposure to blast trauma without head involvement) returning from active service with post-concussive-type problems. New perspectives on such cases and their differentiation from entities such as PTSD (Bhattacharjee, 2008) may offer an opportunity for eye movement testing to provide useful markers of incomplete recovery.

An important point that needs to be considered in the interpretation of the current findings is the limitation of not being able to compare our findings of eye movement impairment in the PCS group to imaging evidence of neural injury in the current sample. However, recent studies using advanced imaging techniques such as diffusion tensor imaging and functional MRI indicate an emerging systematic link between the incidence of persistent post-concussional symptoms and presence of white matter abnormalities as well as abnormal cortical activation patterns (Hofman *et al*., 2002; Salmond *et al*., 2006; Bazarian *et al*., 2007; Chen *et al*., 2008; Lipton *et al*., 2008; Miles *et al*., 2008; Niogi *et al*., 2008). Our findings of suboptimal eye movement function in PCS, and the present suggestions of a contribution of subcortical structures to the observed deficits, fall in line with

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these imaging findings. It will have to be the subject of future studies to further examine the link between eye movement function in PCS and structural changes in the brain. As this is the first study to have examined eye movement function in PCS, such future research and the validation of the current findings by other studies will be vital in advancing a potential clinical use of eye movement testing in PCS.

In conclusion, our findings indicate that eye movement function in PCS does not follow the normal recovery path of eye movements after mCHI, marking ongoing cerebral impairment independently of patient self-report and neuropsychological assessment. Importantly, poorer oculomotor function was unrelated to depression or estimated IQ. Whilst oculomotor and neuropsychological tests partially overlapped in identifying suboptimal brain function, eye movements provided additional evidence of dysfunction in areas such as decision making under time pressure, response inhibition, short-term spatial memory, motor-sequence programming and execution, visuospatial processing and integration, visual attention and subcortical brain function. Indications of poorer subcortical/subconscious oculomotor function in the PCS group support the notion that PCS is not merely a psychological entity but also has a biological substrate. Eye movements might be of particular interest in PCS cases with high symptom load and poor ability to cope with activities of daily living but whose clinical test profile is otherwise unremarkable with regard to neuropsychological testing or other assessments. Eye movement testing, and evidence of suboptimal subcortical functioning in particular, may help demonstrate incomplete recovery of brain function in such cases. Despite the cost-intensive nature of eye movement assessment in terms of required equipment, eye movement testing should be feasible in centres, which have easy access to eye tracking technology.

Acknowledgements

The study was hosted by the Canterbury District Health Board and the University of Otago, Christchurch, New Zealand. We wish to thank these institutions for their support of this research.

Funding

Participants' travel costs and neuropsychological assessment of the controls was funded by the New Zealand ACC (grant number PRS-06-1127E).

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